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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,182	01/18/2002	Pier Giuseppe Pelicci	0380-P02669/US0	6367
110 7590 12/23/2008 DANN, DORFMAN, HERRELL & SKILLMAN 1601 MARKET STREET SUITE 2400 PHILADELPHIA, PA 19103-2307				
EXAMINER				
ANGELL, JON E				
ART UNIT		PAPER NUMBER		
1635				
MAIL DATE		DELIVERY MODE		
12/23/2008		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/937,182

Applicant(s)

PELICCI ET AL.

Examiner

J. E. Angell

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19, 21, 22, 24, 26-38, 42-47 and 52 is/are pending in the application.
- 4a) Of the above claim(s) 1-8, 11, 13-18, 26, 28-35, 38 and 42-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9, 10, 12, 19, 21, 22, 24, 27, 36, 37, 46, 47 and 52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

This Action is in response to the communication filed on 7/11/2008.

The amendment filed 7/11/2008 is acknowledged and has been entered.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Status of the Claims

Claims 1-19, 21, 22, 24, 26-38, 42-47, 52 are currently pending.

Claims 1-8, 11, 13-18, 26, 28-35, 38, 42-45 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/9/2007.

Claims 9, 10, 12, 19, 21, 22, 24, 27, 36, 37, 46, 47, 52 are examined herein.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 9, 10, 12, 19, 36, 37, 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the instant claims encompass agents that are “nucleic acid molecules [that are] capable of hybridizing to a nucleic acid encoding SEQ ID NO: 2” (e.g., see claim 9). As such, the claims encompass a genus of agents that include, but are not limited to, antisense nucleic acid sequences which specifically hybridize to a nucleic acid sequence which encodes SEQ ID NO: 2 and which inhibit p66shc expression. It is noted that the instant claims do not set forth any basic structural elements for the genus of nucleic acids encompassed by the claims. Therefore, given the broadest reasonable interpretation, the claims can encompass a genus of agents that are not structurally related and for which there are no structural elements common to all members of the genus of molecules. Accordingly, no structure-function relationship can be established for the members of the broadly claimed genus. Without a clear structure-function relationship, one of skill in the art would not be able to readily identify which molecules of the claimed genus of agents function as required by the claims, and which ones do not, without performing additional experimentation. Furthermore, the claims could encompass agents that have not yet been identified or created. Therefore, the specification has not adequately described the genus of nucleic acid agents encompassed by the

claims. It is noted that the specification has described antisense nucleic acid sequences which specifically hybridize to a nucleotide sequence which encodes the p66shc protein that is SEQ ID NO: 2 and inhibits expression of p66shc; however, the instant claims are not limited to these antisense nucleic acid sequences.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of agent encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 9, 10, 12, 19, 21, 22, 24, 27, 36, 37, 46, 47, 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of p66shc expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of p66shc expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of p66shc in cells or tissues comprising contacting said cells or tissues with nucleic acid compositions that hybridize to sequences encoding p66shc (SEQ ID NO:2). The claims of the above invention are also drawn to methods of treating an animal having vascular complications of diabetes, wherein said compositions are administered to animals such that expression of p66shc is inhibited. The language of said claims encompasses both *in vivo* and *in vitro* activity. The specification discloses a working example where the p66shc gene is knocked-out in MEF cells (*in vitro*), as well as in transgenic mice (*in vivo*) wherein p66shc is not expressed due to disruption of the p66shc gene.

The specification does not provide any working examples demonstrating that antisense nucleic acid sequences can be effectively used in an animal to block p66shc expression sufficient to result in the required outcome (e.g., treatment of disease, increase in resistance to oxidative stress, decrease in ROS). Furthermore, the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of

using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its gene disruption models is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. It is acknowledged that one of skill in the art would recognize that antisense oligonucleotides could be used to inhibit expression of a target gene *in vitro*, in non-therapeutic methods, with a reasonable expectation of success.

The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and

immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; “even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism” (Pg. 4503, para. 1 and 2). Branch affirms that “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), while Tamm et al. states that “[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally” (page 493, right column).

Further, Branch reasons that “the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available” (Page 46, second column). Tamm et al. concludes by stating that until “the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach.”

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of p66shc expression *in vivo* using gene disruption techniques as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases suspected of being associated with p66shc expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Furthermore, as indicated above, the *in vivo* results indicated in the working examples were obtained in knock-out mice. It is noted that Crystal (1995) teaches, "Humans are not simply large mice", and points out that, "predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (see pg 409, col. 1-2). Therefore, results obtained in mice cannot be extrapolated to humans with a reasonable expectation of success.

The claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing a condition or disease suspected of being associated with p66shc expression in humans. Since the specification fails to provide any guidance for the successful treatment or prevention of such a disease, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would

have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and/or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Response to Arguments

3. Applicant's arguments filed 5/8/2008 have been fully considered but they are not persuasive with respect to the pending rejections.
4. Applicants argue that the claims have been amended to encompass a nucleic acid agent where in certain dependent claims the nucleic acid agent is an antisense nucleic acid sequence.
5. This is not persuasive because although the claims now read on a nucleic acid agent, the broad claims are not limited to an antisense nucleic acid agent. The instant disclosure does not provide the required written description of the genus of nucleic acid agents encompassed by the claims for the reasons indicated above. Therefore, Applicants arguments are not persuasive.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635